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Evolution of renal function and predictive value of serial renal assessments among patients with acute coronary syndrome: BIOMArCS study

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ABSTRACT

Background: Impaired renal function predicts mortality in acute coronary syndrome (ACS), but its evolution immediately following index ACS and preceding next ACS has not been described in detail. We aimed to describe this evolution using serial measurements of creatinine, glomerular filtration rate [$eGFR_{Cr}$] and cystatin C [CysC].
Methods: From 844 ACS patients included in the BIOMArCS study, we analysed patient-specific longitudinal marker trajectories from the case-cohort of 187 patients to determine the risk of the endpoint (cardiovascular death or hospitalization for recurrent non-fatal ACS) during 1-year follow-up. Study included only patients with $eGFR_{Cr} \geq 30$ ml/min/1.73 m^2. Survival analyses were adjusted for GRACE risk score and based on data >30 days after the index ACS (mean of 8 sample per patient).
Results: Mean age was 63 years, 79% were men, 43% had STEMI, and 67% were in eGFR stages 2–3. During hospitalization for index ACS (median [IQR] duration: 5 (3–7) days), CysC levels indicated deterioration of renal function earlier than creatinine did (CysC peaked on day 3, versus day 6 for creatinine), and both stabilized after two weeks. Higher CysC levels, but not creatinine, predicted the endpoint independently of the GRACE score within the first year after index ACS (adjusted HR [95% CI] per 1SD increase: 1.68 [1.03–2.74]).
Conclusion: Immediately following index ACS, plasma CysC levels deteriorate earlier than creatinine-based indices do, but neither marker stabilizes during hospitalization but on average two weeks after ACS. Serially measured CysC levels predict mortality or recurrence of ACS during 1-year follow-up independently of patients' GRACE risk score.

1. Introduction

Renal dysfunction, including mild renal impairment (eGFR 60–89 ml/min/1.73 m^2) [1,2], is strongly associated both with short- and long-term mortality in patients with ST elevation myocardial infarction (STEMI) and in those with non-STEMI [3–5]. Patients with chronic kidney disease (CKD) are often treated less aggressively for acute coronary

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syndrome (ACS) than those without CKD [3,4,6]. However, even if they are on optimal therapy they will still have poorer prognosis [7]. Renal dysfunction is associated with coronary atherosclerosis, including higher coronary plaque burden, plaques containing greater necrotic core and more dense calcium, as well as with abnormalities of cardiac muscle, including left ventricular hypertrophy, dilated cardiomyopathy, and systolic dysfunction [8–10]. Several studies have shown that specific comorbidities such as hypertension, diabetes, and dyslipidemia, contribute both to cardiovascular and renal damage [11,12]. Neurohormonal activation is also affected after ACS [13–15], and angiotensin II may influence deterioration of both cardiovascular and renal functioning [13,16,17].

In heart failure (HF), renal dysfunction has been identified as the most prevalent comorbidity and strongly predicted adverse clinical outcomes [18,19]. Worsening renal function has also been used as the primary endpoint in several clinical trials in acute HF [20,21].Underlying hemodynamic dependence between the heart and kidneys including renal perfusion hemodynamics and systemic neuro-hormonal activation, has been identified as the main driver of such a relationship [22].

In spite of these overlapping pathophysiological aspects between the heart and kidneys, the detailed temporal evolution of renal function immediately following index ACS, and preceding a recurrent ACS, has not yet been described. Existing studies have mostly assessed renal function only at a single time point to investigate its prognostic value, and have used for example time of admission, a moment during in-hospital stay or time of discharge as 'study baseline'. However, it is unclear whether a patient's renal function examined at these time points during hospitalization reflects "true" renal functioning or whether it is temporarily disturbed by the index ACS. Moreover, it remains unknown at which moment after ACS renal function stabilizes. Knowing these temporal patterns may help us in expanding our understanding of renal dysfunction in patients with ACS, and thereby aid in identifying high-risk subgroups.

The aim of our study was two-fold: (1) to describe the evolution of renal function from its initial change during ACS until stabilization, according to the kinetics of several renal function parameters (plasma creatinine, estimated glomerular filtration rate [$eGFR_{Cr}$], and cystatin C [CysC]), (2) to investigate the predictive value of serial renal marker assessments within the first year after index ACS. For the latter purpose, we also examined whether rates of change of these renal markers are relevant for clinical risk prediction in ACS.

2. Methods

2.1. BIOMArCS

BIOMArCS is a multi-centre prospective study conducted in 18 Dutch hospitals [23]. Details on the BIOMArCS design are reported elsewhere [24]. Briefly, we included patients who were hospitalized for ACS including STEMI, non-STEMI, and unstable angina pectoris (UAP), with ≥1 cardiovascular risk factor (Table S1); $eGFR_{Cr} < 30$ ml/min/1.73 m^2 was an exclusion criterion because of the potential influence of renal clearance on certain biomarkers investigated in the BIOMArCS cohort [24]. All patients were treated according to prevailing guidelines and at the discretion of the treating physician. The study protocol has been approved by the Institutional Review Board of all participating hospitals and written informed consent was obtained from all patients.

2.2. Selection of patients to analyse the relation between renal markers and repeat ACS

For the analysis of the relation between (renal) biomarkers and repeat ACS during 1-year follow-up, we applied a case-cohort design, which allowed a comparison of all study endpoint cases to a limited random sample of non-cases (instead of all non-cases), thereby increasing the study's efficiency [25]. For this purpose, after study completion (i.e., inclusion, follow-up, and study endpoint adjudication) a sub-cohort of 150 patients was randomly sampled from the parent cohort ($n = 844$), using a computer generated random sampling procedure. Subsequently, all patients who experienced the endpoint, but who were not a part of the random sub-cohort were added (37 cases), so that the case-cohort comprised 187 patients (Fig. 1). Thus, we analysed all cases, but analysed only those non-cases (non-endpoint patients) who were present in the random sub-cohort.

2.3. Selection of patients to analyse the washout of renal markers immediately following index ACS

To enable a precise description of early washout biomarker patterns, a total of 68 (8%) BIOMArCS patients underwent additional blood sampling at 24, 48, 72 and 96 h after the index ACS. We excluded the 6 patients who experienced the study endpoint within the first two month due to potential influence on stabilization of the washout pattern, and enriched with the endpoint-free patients from the random sub-cohort. Thus, a total of 185 patients were available for the analysis of washout patterns of renal biomarkers (Fig. 1).

2.4. Follow-up visits and blood sample collection

Blood samples were collected at admission, hospital discharge, and every two weeks after index ACS during the first six months, followed by monthly collection until one year (Fig. 1). A visit window of ±1 week was allowed, and a maximum of two consecutive visits were allowed to be skipped (for personal reasons). If logistic reasons hindered inclusion during hospitalization, patients could be included on the first outpatient visit within six weeks after discharge; the sampling schedule was then adapted accordingly. A trained research nurse interviewed the patients at each visit and obtained data on anginal status (Canadian Cardiovascular Society classification), HF symptomatology (New York Heart Association classification), and factors that might influence biomarker levels, e.g. smoking, occurrence of infections, inflammatory or allergic responses, alterations in medication, interventional or operative procedures and hospital admission. Blood samples were processed on-site and transported batch-wise under controlled conditions to the department of Clinical Chemistry of the Erasmus MC, Rotterdam where they were stored until analysis was performed.

Glomerular filtration rate (GFR) was determined by the Modification of Diet in Renal Disease (MDRD) Study equation [26]. Patients were categorized using the modified eGFR definition from the National Kidney Foundation – Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines [27].

2.5. Analysis of renal markers

In the 187 case-cohort patients and in the 185 patients that comprise the washout analysis set, renal biomarkers (creatinine and CysC) were measured batch-wise at the laboratory of the department of Clinical Chemistry and Hematology of the University Medical Center Utrecht. Creatinine was measured on clinical routine equipment (AU5800, Beckman Coulter, Brea, CA, USA). Cystatin C was measured by ELISA following manufacturer's instructions (mouse-anti human DuoSet DY1196, R&D Systems, Oxon, UK; inter- and intra-assay CV <10%). The EDTA-plasma was used for biomarker analysis. Importantly, laboratory personnel were blinded to any patient data and scope of the study, whereas biomarker measurements did not interfere with treatment.

2.6. Study endpoints

The study endpoint was a composite of cardiac mortality or a diagnosis of a non-fatal myocardial infarction or unplanned coronary revascularization due to progressive angina pectoris during 1-year follow-up. Any death was considered cardiac unless documented otherwise. Incident non-fatal myocardial infarction was defined as the combination of typical ischemic chest complaints and objective evidence of myocardial ischemia or myocardial necrosis as demonstrated by the ECG and/or elevated cardiac markers. The criteria for non-fatal myocardial infarction during follow-up were the same as those for the index event (Table S1, points 1 and 2 of the inclusion criteria). A Clinical Event Committee, blinded for the renal biomarker results, reviewed hospital records and discharge letters and adjudicated the study endpoints.

3. Statistical analysis

3.1. Case-cohort – prediction of events

Categorical baseline data are summarized by percentages, and continuous data by medians and 25th–75th percentiles. Differences between cases and non-cases were evaluated by classical statistical tests, as specified in the caption of Table 1.

To obtain valid inferences for the relation between the temporal evolvement of a biomarker and the incidence of the study endpoint, the longitudinal- and event-processes must be jointly modelled [28]. We applied Bayesian semiparametric joint models for this purpose, which combine linear regression and Cox proportional hazard regression. Linear mixed-effects (LME) models were used to describe patient-specific longitudinal biomarker trajectories B(t) as a function of time (t). Non-linear trajectories were modelled by cubic splines. ^{2}Log-transformations of biomarker values were used to assure normal distributions of regression residuals. More specifically, the unit of analysis was the Z-score (i.e. the standardized form) of the ^{2}log-biomarker, which allows a direct

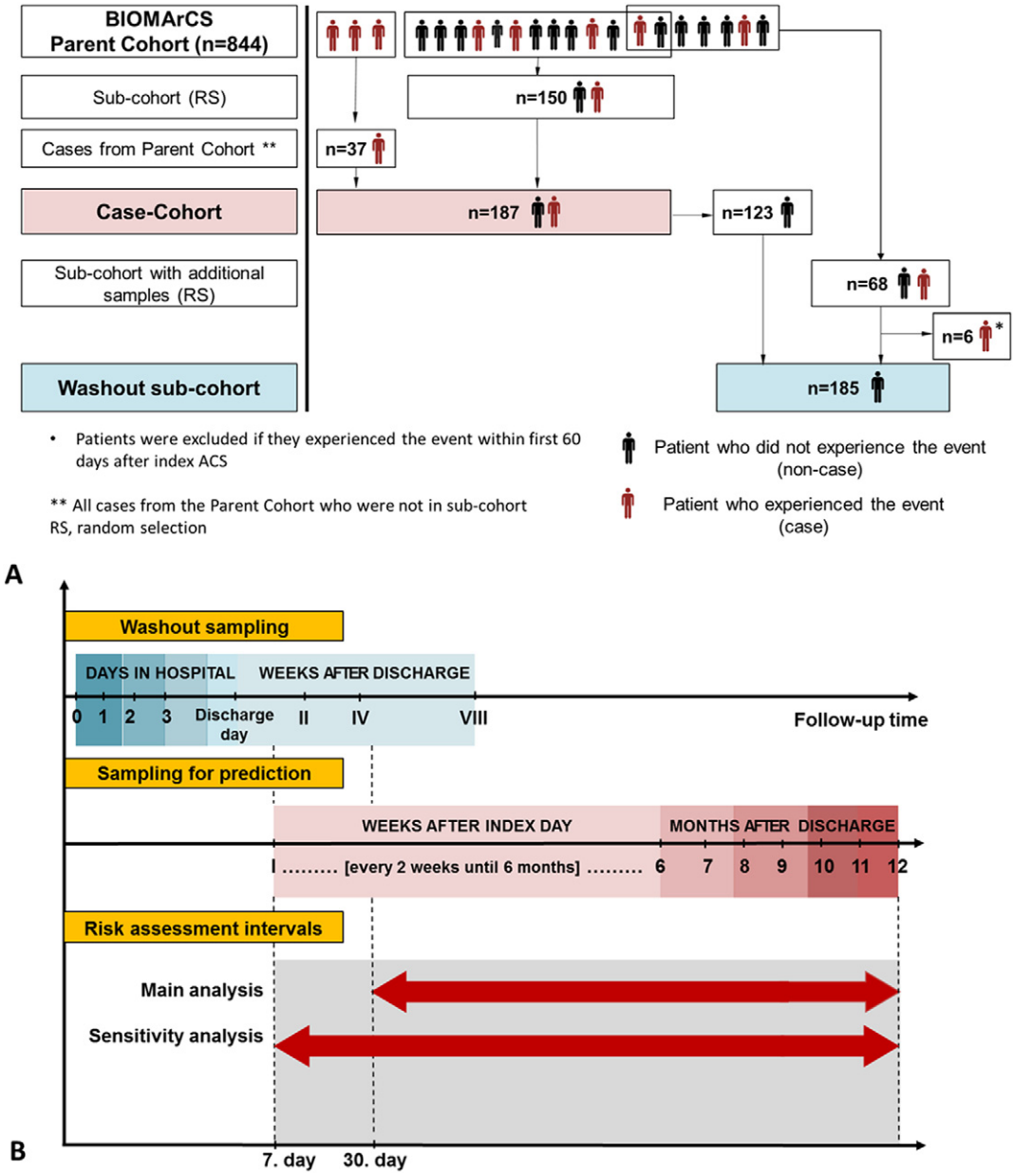

Fig. 1. Participants flow chart, study design, and sampling schema. **Legend**: Case-Cohort was constructed from a random sample of 150 patients from the full cohort ($n = 844$, all enrolled patients) and enriched with all cases ($n = 37$). For the case-cohort, blood samples were collected at admission, at hospital discharge, and subsequently every two weeks during the first six months, followed by monthly collection until 1 year (*sampling for prediction*). Risk assessment time intervals were: (1) Main analysis >30 days until study endpoint or last sample moment, (2) Sensitivity analysis >7 days until study endpoint or last sample moment. Washout sub-cohort was constructed from a random sample of 68 patients from the parent cohort in whom additional samples were collected within 24, 48, 72 and 96 h after admission, at the day of hospital discharge, and at 2, 4 and 8 weeks (*washout sampling*). Patients who experienced new events within the first 60 days form the index ACS were excluded due to potential influence on stabilization of the washout pattern ($n = 6$). The washout sample was then enriched with 123 patients who did not experience incident events from the sub-cohort of 150 random patients, resulting in a total of 185 patients for the washout sub-cohort.

comparison of the effects of separate markers. Results are presented as hazard ratios (HR) and corresponding 95% confidence intervals (CI) for a 1SD difference of the biomarker on the log-scale.

The LME models not only provide unbiased estimates B(t) of the biomarker level at timepoint t, but also of its instantaneous rate of change (or: slope) B′(t) at t, that corresponds to the first derivative of B(t). Since we also aimed to study rate of change, we also provided HRs for the instantaneous slope of the marker's trajectory. Further details on this method of dynamic prediction modeling were described elsewhere [29]. Results are presented as HRs (95% CIs) for a 0.1 SD difference of the marker's rate of change on the log-scale.

Analyses were first performed univariably, and subsequently multivariable adjustment was performed. For this purpose, the GRACE risk score for assessment of post-discharge death and myocardial infraction, as recommended by international guidelines [30–32], was used. This specific GRACE risk model consists of age, first troponin (or CKMB) after discharge, history of MI, congestive HF and whether CABG was performed at the index hospitalization [33]. The survival model was adjusted for the GRACE risk score, and the LME model was adjusted for GRACE risk score, sex, diabetes, history of coronary artery bypass surgery, history of valvular heart disease, history of stroke, history of peripheral arterial disease.

To describe the average evolution of renal function during the year preceding death or the recurrence of ACS, we analysed all available data >30 days after the index ACS until the endpoint or last sample moment.

Table 1
Baseline characteristics of the parent cohort and case-cohort set.

Characteristics	All patients	Case-cohort		
		Non-cases	Cases	*p*-Value
Number of patients	844	142	45	
Presentation and initial treatment				
Age, years, median (IQR)	62.5 (54.3, 70.2)	62.6 (55.0–70.9)	67.4 (57.1–76.5)	0.07
Male sex, %	77.9	78.2	80.0	0.79
Admission diagnosis, %				0.46
STEMI	51.7	45.8	35.6	
NSTEMI	37.7	39.4	48.9	
UAP	10.6	14.8	15.6	
Culprit artery, %				
RCA	33.1	34.5	26.7	0.33
LM	2.5	3.5	2.2	1.00
LAD	31.9	33.8	31.1	0.74
LCX	16.5	12.0	20.0	0.17
CAG performed, %	94.4	93.7	89.0	0.33
PCI performed, %	86.3	82.6	87.2	0.49
CK_{max}, U/L median (IQR)	513 (200-1370)	449 (190-1197)	389 (194-1122)	0.78
Killip class, %				0.012
Class I		94	82	
Class II		4	16	
Class III		2	0	
Class IV		0	2	
Renal function on admission				
Urea, mmol/L median (IQR)		5.9 (5.0–7.0)	6.8 (4.7–7.9)	0.19
Creatinine, μmol/l median (IQR)		82 (69–95)	87 (73–93)	0.22
eGFR, ml/min/1.73 m^2 median (IQR)		83 (69–98)	78 (71–92)	0.21
KDOQI classification, (%)				
eGFR ≥90 ml/min/1.73 m^2		35	24	0.16
eGFR 60–89 ml/min/1.73 m^2		55	60	
eGFR 30–59 ml/min/1.73 m^2		10	16	
Medical history, %				
Diabetes mellitus	23.5	16.9	37.8	0.003
Hypertension	55.5	54.2	48.9	0.53
Dyslipidemia	49.3	50.7	44.4	0.46
Prior PCI	26.2	27.0	31.1	0.59
Prior CABG	10.0	8.5	24.4	0.004
Prior MI	26.9	30.3	31.1	0.92
Heart failure	2.4	2.8	8.9	0.097
Valvular heart disease	2.2	1.4	8.9	0.031
Prior CVA/TIA	9.0	11.3	20.0	0.13
PAD	8.9	6.3	22.2	0.004
Medication at first blood sampling moment from 7 days after index ACS, %				
Aspirin	95.1	93.0	100	0.20
P2Y12 inhibitor	94.8	90.4	96.8	0.46
Vitamin K antagonist	6.9	7.9	9.7	0.72
Statins	95.8	95.6	96.8	1.00
Beta-blocker	90.1	85.1	93.5	0.37
ACE inhibitor or ARB	83.6	84.2	90.3	0.57

ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass grafting; CK_{max}: maximum creatine kinase during the index admission; LAD: left anterior descending artery; LCX: left circumflex artery; LM: left main coronary artery; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction; SD: standard deviation; $Troponin_{max}$: maximum troponin value during the index admission; UAP: unstable angina pectoris.

To investigate the predictive value of repeatedly measured markers, we analysed all available data >30 days after the index ACS event, to ensure that all biomarkers were then stabilized. Additionally, a sensitivity analysis was performed on all repeated measurements >7 days after the index ACS. Measurements that were obtained within 7 days after index ACS were excluded to avoid biased estimates due to elevated biomarkers induced by the index ACS.

3.2. Analysis of evolution of renal function during the washout phase (immediately following index ACS)

LME models were applied to investigate at which time point the renal markers reach their highest point (creatinine, CysC) or lowest point ($eGFR_{Cr}$) and at which time point they return to stable levels. All renal biomarkers were ^{2}log transformed, and non-linear evolutions (for the fixed- and random-effects parts) were modelled by restricted cubic splines. We optimized the position of the spline knots by using Akaike information criteria and Bayesian Information criteria. After obtaining optimal evolution curves representing the washout patterns of the renal markers, we calculated the maximum or minimum of these curves to determine the time point of the peak or nadir. To determine the moment of marker stabilization, we also numerically compared the deltas of biomarkers between every two consecutive blood samples (a difference <1% signified a stabilization).

R statistical software (version 2.15.0) was used for advanced statistical analyses, in particular the package JMbayes [14]. All statistical tests were two-tailed and *p*-values <0.05 were considered statistically significant.

4. Results

4.1. Study endpoints and baseline characteristics

Of 844 enrolled patients, 45 reached the study endpoint during a median (IQR) follow-up of 11.5 (2.7–12.1) months. Baseline characteristics of all patients in the BIOMArCS study and in the case-cohort set are shown in Table 1. In the case-cohort, on admission mean (±SD) age was 63 (±11) years, 79% were men, 43% had STEMI, 42% had non-STEMI, and 15% had UAP. The median (IQR) $eGFR_{Cr}$ was 81 (70–98) ml/min/1.73 m^2, and 33% of patients were in eGFR stage 1 (GFR ≥ 90), 56% in stage 2 (GFR 60–89), and 11% in stage 3 (GFR 30–59).

4.2. Average evolution of renal markers immediately following index ACS

A total of 687 samples were drawn from the 185 non-endpoint patients that comprise the washout analysis set, with a mean of 4 samples per patient. Average washout evolutions of plasma creatinine, $eGFR_{Cr}$ and CysC are shown in left panel of Fig. 2. The figure shows that CysC levels reached a peak on the 3rd day after index ACS. This was followed by a nadir of $eGFR_{Cr}$ on the 4th day, and a peak of creatinine levels on the 6th day. We also found different time intervals from the highest or lowest point to stabilization for these markers: CysC – 11 days (stabilized on day 13), $eGFR_{Cr}$ – 10 days (stabilized on day 13) and creatinine – 8 days (stabilized on day 14). Nevertheless, the stabilization of the markers after index ACS appeared to be temporary.

4.3. Average evolution of renal markers during the year preceding death or next ACS

In the time-period >30 days after index ACS, a total of 1117 blood samples were collected from 158 of the 185 patients that comprise the case-cohort, with a median of 7 samples per patient - the remaining 27 patients (17 study endpoint cases) only had samples in the 0–30 day time window. Although plasma creatinine levels increased slightly prior to the incident event in patients who ultimately reached the study endpoint, substantial overlap was present between average evolutions of these patients and those who remained endpoint-free (Fig. 2: right panel). $eGFR_{Cr}$ displayed similar dynamics, but with a smaller overlap. Notably, plasma CysC showed substantially higher levels during follow-up in patients ultimately reaching the study endpoint.

4.4. Predictive value of renal markers during the year preceding death or next ACS

Higher levels of CysC assessed at any point in time during follow-up were positively associated with the endpoint (HR [95% CI]: per 1SD increase of ^{2}logCysC: 1.79 [1.21–2.63], $p = 0.006$). After controlling for the GRACE risk score, CysC level remained a significant predictor (adjusted HR [95% CI]: 1.63 [1.01–2.66], $p = 0.043$).

In the sensitivity analysis, CysC level measured serially >7 days after the index ACS was slightly weaker, but also a significant predictor (1.68 [1.13–2.46], $p = 0.009$). After adjustment for the GRACE risk score, the risk estimates remained materially the same (adjusted HR [95% CI]: 1.63 [1.01–2.57], $p = 0.045$) (Table S2).

No clear associations were found between serially assessed plasma creatinine or $eGFR_{Cr}$ and the study endpoints (Table 2).

None of the slopes of the renal markers trajectories were associated with the endpoint (Table 2, and Table S2).

5. Discussion

In this prospective multicenter study, we sought to describe the longitudinal trajectories of different renal markers, and their impact on 1-year cardiac outcome in patients with ACS. We found that plasma CysC levels predict mortality or recurrence of ACS within the first year independently of patients' GRACE risk score. We also found that CysC levels deteriorate earlier than creatinine-based indices do during index ACS. Importantly, we observed that both renal markers usually do not stabilize during hospitalization, but on average two weeks after index ACS. Altogether, these findings underscore the relation of renal dynamics with ACS, and carry implications for the monitoring of renal function in these patients.

The majority of studies in patients with ACS have focused on prognostic value of creatinine levels or eGFR assessed at one point in time. However, the prognostic value of serial renal assessments, including CysC levels, is less clear and has mainly been investigated in patients

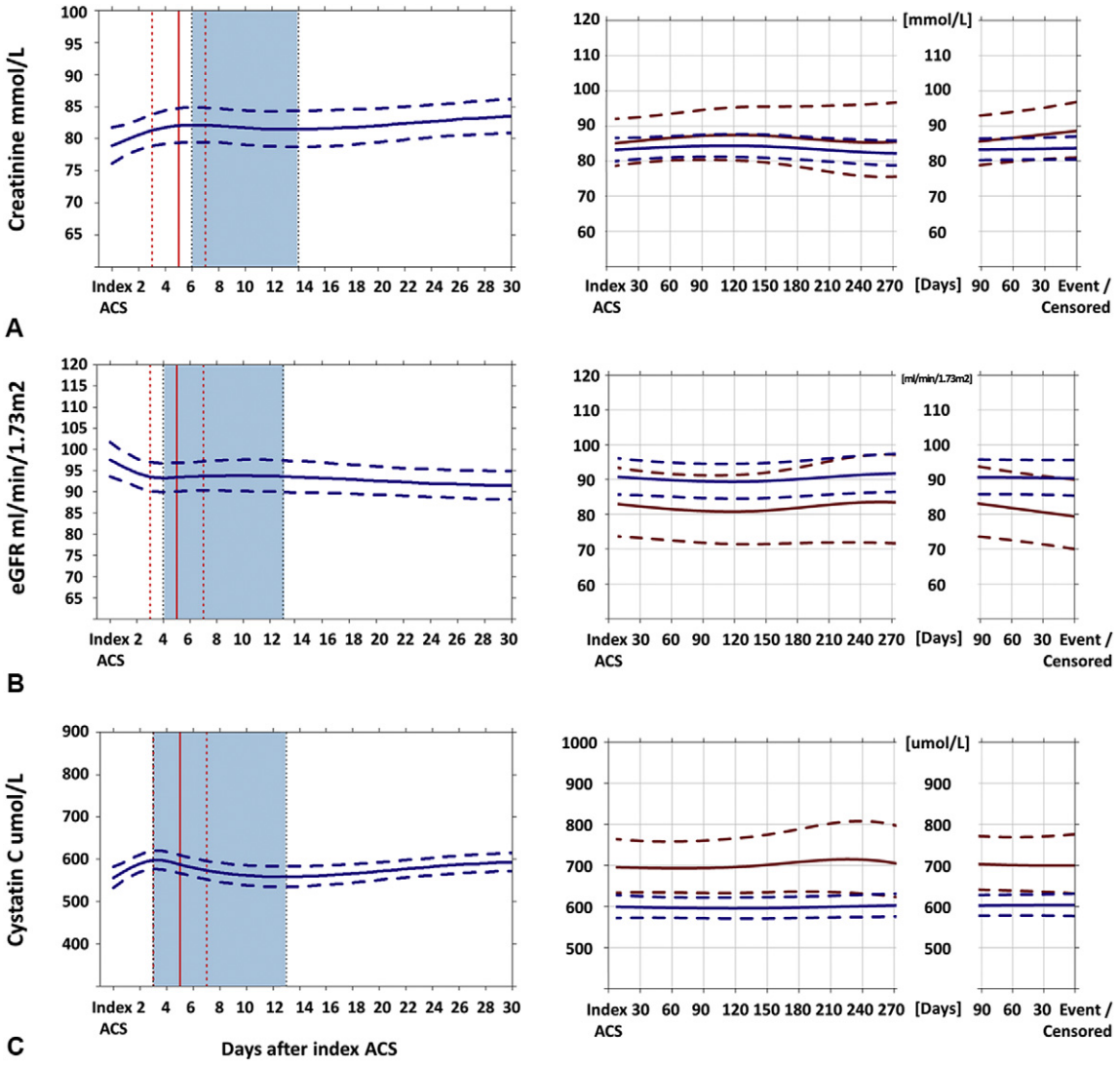

Fig. 2. Average evolution of renal markers immediately following index ACS and during the year preceding death or recurrence of ACS or last sample moment. **Legend**: Left panel: the follow-up time (days) starting from admission is displayed on the x-axis. Renal marker levels are displayed on the y-axis. The solid red line depicts the median discharge day from hospital with corresponding interquartile range (dashed red lines). The left black dashed line displays time of the highest peak of plasma creatinine and cystatin C and the lowest peak of eGFR, and the right black dashed line displays the time moments of biomarker stabilization. The light blue area (between the two black dashed lines) represents the time period from the peaks/nadirs to stabilization. Right panel: the solid red line depicts the average evolutions of renal markers in patients who reached the endpoint, and the solid blue line depicts the evolutions in endpoint-free patients. The dashed lines represent the 95% confidence interval. A. plasma creatinine (mmol/L); B. eGFR (ml/min/1.73 m^2); C. plasma cystatin C (μg/ml).

Table 2
Hazard ratios for the primary endpoint in relation to serially assessed marker levels >30 days after index ACS.

	Geometric mean[e]			Levels[a]		Instantaneous slope[b]	
	Mean − 1 SD	Mean	Mean + 1 SD	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Creatinine	67	84	105				
Crude model				1.28 (0.84–1.97)	0.28	1.00 (0.53–1.85)	0.98
+GRACE risk score[c,d]				1.12 (0.73–1.76)	0.61	1.00 (0.53–1.89)	0.99
eGFR	64	88	120				
Crude model				1.52 (0.97–2.37)	0.06	1.00 (0.53–1.86)	1.00
+ GRACE risk score[c,d]				1.32 (0.85–2.10)	0.20	1.02 (0.56–1.87)	0.93
CysC	473.1	613.1	794.6				
Crude model				1.79 (1.21–2.63)	0.006	0.99 (0.53–1.90)	0.98
+GRACE risk score[c,d]				1.63 (1.01–2.66)	0.043	0.99 (0.53–1.83)	0.99

[a] Hazard ratios (HRs) and 95% confidence interval (CI) are given per 1-SD increase (creatinine and cystatin C), and 1-SD decrease (eGFR) on the 2-log scale at any time point after 30 days after index ACS.
[b] HRs (95%) CI are given per 0.1-SD increase in the slope (creatinine and cystatin C), and 0.1-SD decrease (eGFR) on the 2-log scale at any time point after 30 days after index ACS.
[c] Longitudinal model adjusted for GRACE risk score, sex, diabetes, history of coronary artery bypass surgery, history of valvular heart disease, history of stroke, history of peripheral arterial disease.
[d] Survival model adjusted for GRACE risk score. GRACE risk score is calculated as the weighted sum of age, first troponin after discharge, history of MI, congestive HF and whether CABG was performed at the index hospitalization.
[e] Geometric mean ± 1 standard deviation (SD) of the patient-specific biomarker values after 30 days (presented on the linear scale).

with HF [19,34]. In acute HF, studies have shown that worsening renal function during hospitalization entails poor prognosis especially if a patient's clinical status deteriorates simultaneously [35]. Otherwise, small to moderate renal function decline during hospitalization in the setting of aggressive diuresis may simply be result of decongestion and clinically benign [36,37]. In chronic HF, serial measurements of creatinine and CysC during outpatient follow-up strongly predicted long-term adverse clinical outcomes such as HF rehospitalization and death [34].

In patients with ACS, some authors [38] have speculated that assessment of renal function should be repeated after hospital discharge to ensure that 'true' renal functioning is detected, and not transient renal fluctuations. However, no study has examined the evolution of renal function during the washout phase early after ACS and during 1-year follow-up. It is here that our study further extends existing evidence. Our findings suggest incremental value of CysC levels for risk assessment by means of the GRACE score. These findings are also supported by Correa et al. [39], who found that CysC levels predicted cardiovascular death or HF hospitalization in patients after ACS, independently of established cardiovascular risk predictors including troponins and brain natriuretic peptide. Interestingly, Correa et al. collected samples at a median of 14 days after ACS. This underpins findings from our washout cohort, indicating that CysC level usually stabilizes on average two weeks after ACS. Taken together, it seems reasonable to re-assess CysC levels in the time period after hospital discharge in patients for whom a more complete risk assessment is required.

Previous studies that also used repeated CysC measurements are scarce. Akerblom et al. assessed whether repeatedly measured CysC levels (at baseline, discharge, and the mean value of both measurements) carry predictive value in 4295 patients with ACS and similar baseline creatinine levels as those in our study [40]. They reported that serial CysC assessment did not improve risk prediction. However, our results were obtained using a different approach. Contrary to Akerblom et al., we examined long-term temporal evolution of renal markers, specifically by using repeated measurements up to 1 year after hospital discharge to estimate the CysC trajectories in each patient. We then jointly modelled these renal trajectories with time-to-event analysis. This joint modeling approach carries several advantages. It enabled us to investigate the association with adverse events in a less biased way [41]. It also allowed us to examine the associations between the rates of change of different renal function parameters and adverse events. The latter analyses suggested that although CysC levels contribute to a patient's clinical risk, their rates of change do not. This is supported by Shlipak et al. who also could not demonstrate a significant association between change in creatinine (delta-creatinine ≥0.3 mg/dl) and outcomes in patients with stable coronary artery disease (CAD) in the Heart and Estrogen/Progestin Replacement Study (HERS) [42]. Thus, it appears that rate of change of renal function is only relevant for clinical risk in patients with CAD and systolic dysfunction, or with HF [19,34,38].

Although we observed a slight deterioration of creatinine-based estimates prior to the incident endpoint, we could not confirm their predictive value as found previously [1,2]. This may be explained by the relatively low prevalence of patients with more severe renal dysfunction in our study. In fact, only 11% of our patients had moderate renal impairment ($eGFR_{Cr}$ 59–30 ml/min/1.73 m^2) and there were no patients with $eGFR_{Cr}$ < 30 ml/min/1.73 m^2 due to the exclusion criteria. However, it appears that CysC levels were still able to detect these subtle differences, which may be of particular interest for patients with mild $eGFR_{Cr}$ reduction ($eGFR_{Cr}$ 60–89 ml/min/1.73 m^2), as was the case in 56% of patients included in the study. Indeed, studies have shown that CysC levels correlate more closely with the true GFR than serum creatinine levels [43–45]. Although a possible non-renal link between CysC and cardiovascular risk has been suggested [46], a recent Mendelian randomization study by Van der Laan et al. could not substantiate a causal role of CysC in etiology of cardiovascular disease [47]. Finally, although such mild renal dysfunction usually does not require specific management, accurate monitoring of these subtle differences by CysC may carry potential for improving risk stratification of these patients.

5.1. Study limitations

Several aspects of our study warrant consideration. First, the MDRD equation, although validated in patients with ACS, has limitations due to the non-renal factors that influence creatinine measures. Likewise, proteinuria was not measured in this cohort. Nevertheless, we chose MDRD because it is the most widely utilized $eGFR_{Cr}$ equation, and thus enables comparisons with existing studies. Second, patients were excluded in case of $eGFR_{Cr}$ < 30 ml/min/1.73 m^2, which limits generalizability of our results to the ACS population at large. Yet we were able to demonstrate, even in this ACS population with a lesser degree of renal impairment, that renal dysfunction quantified by plasma CysC is associated with cardiovascular events. Third, despite controlling analyses for GRACE risk score, a risk model recommended in international guidelines, residual confounding may still be present.

6. Conclusion

Immediately following index ACS, plasma CysC levels deteriorate earlier than creatinine-based indices do, but neither marker stabilizes

during hospitalization but on average two weeks after ACS. Serially measured CysC levels predict mortality or recurrence of ACS within the first year independently of GRACE risk score.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.052.

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